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Chemical processes and products

The present invention relates to novel, orally effective analgetic compositions, which do not produce analgesia, euphoria or physical dependence (addiction) after parental administration. In particular, the invention relates to compositions, which comprise an orally ineffective dose of "naloxone" and an orally effective, strong analgetic in an oral dosage form, and which contain a sufficient amount of naloxone for each analgetic dose of the analgetic agent in order to negate the analgesia-, euphoria- and dependence-producing action of the composition when the oral dosage form is administered parenterally.

US patent 3 254 088, wherein the preparation of naloxone and its action as antagonist to a narcotic is described, belongs to the prior art.

US patent 3 493 657 describes the combination of morphine and naloxone as a composition for parenteral administration, "which has strong analgetic as well as antagonistic action without the occurrence of undesired or dangerous side effects." An article in the NEW YORK TIMES dated July 14, 1970 describes the oral administration of naloxone to narcotic-addicts as method of treatment. The oral administration of naloxone (in high doses) "renders it impossible for the addict, to experience a "high", independent of the amount of heroine, the addict is using". The compositions according to the present invention, which are orally effective analgetic compositions, which do not produce analgesia, euphoria or physical dependence when administered parenterally, are not at all obvious from the prior art.

Abuse of drugs has almost become a way of life for a rapidly growing part of the world's population, particularly here in the United States. It became fashionable for many of the younger generation to experiment with any kind of drug, which produces an emotional, psychological, euphoric, depressive or in general psychedelic experience.

Most of the drugs used for such illegal purposes comprise the barbiturates, lysergic acid diethylamide (LSD), mescaline, marihuana (tetrahydrocannabinol), strong analgetics, (heroin, codeine, morphine, meperidine, propoxyphen [darvone], methadone, dihydrocodeinone, pentazocine and the like), stimulants for the central nervous system, (amphetamines and the like) and some of the major or minor tranquilizers, (promazines, meproamate, diazepines and the like). Most of these compounds are generally used in medicine for the legal treatment of different conditions and are thus available on the market, although in restricted way. Although said compounds are a necessary part of modern medicine, it would be highly desirable to firstly produce new drugs, which do not mislead to drug abuse or, secondly, to "denaturate" (to change their features) the known substances in order to avoid their illegal use.

For many years, the pharmaceutical industry tried to solve the first goal, but unfortunately was not very successful. Focussing on the strong analgetics, it is obvious that a lot of money and effort were spent to produce chemicals, which display a good analgetic efficacy, but have little or no addictive liability. Although good progress was made, see e.g. the development of propoxyphene as a substitute for codeine or pentazocine as the substitute for morphine or meperidine, said substances are still described in the medical literature as addictive and/or euphoric and subjected to the abuse by parenteral administration. Furthermore some of these substances show undesired side effects, e.g. bad hallucinations, etc.

It is known to the "narcotic enforcement agencies" and others in the medical field that a considerably large amount of the strong analgetics, which are intended for legal medical use, is offset by illegal or careless action, in most cases the addict or potential addict obtains said substances by theft or by careless prescription methods of the physician.

It is known from experience that the actual addict satisfies his/her addiction by the parenteral way (mainlining) in order to gain maximal euphoric action. The potential addict or curious person will experiment in the same way too. Unfortunately, a substantial amount of the legal strong analgetics, which are formulated in an oral dosage form, are offset for parenteral use and abuse. Because the oral dosage forms of these drugs, which have been offset from legal sources, have to be usable in a parenteral way in order to produce the desired euphoria, it follows that, if these oral dosage forms are rendered ineffective or unpleasant for parenteral use by any means, this special supply of euphoric drugs is taken away from the addict or the potential addict.

Naloxone, chemically 1-N-allyl-14-hydroxynordihydromorphinone (Merck Index, 8th edition, page 712, Merck & Co., Rahway, New Jersey, USA patent 3 254 088 [1966]), is a strong narcotic-antagonist when administered parenterally. The parenteral product can be used for the treatment of narcotics-overdoses or in order to detect an addiction. Although naloxone is parenterally very effective (a parenteral dose of 0.1 mg up to 2.5 mg induces withdrawal symptoms of narcotics in the addict or results in a compensation effect of the narcotic in case of overdoses), the compound has to be administered in 200 to 400-times larger amounts than the parenteral dose in order to orally result in the same effect.

It is known that the concomitant parenteral administration of equivalent therapeutic doses of naloxone and a euphoria-producing narcotic or narcotic-like analgetic negates the analgetic and euphoric effects in a normal individual and the euphoric and/or maintenance effect of the analgetic in an addict.

Many interchangeable terms are generally used in order to describe the psychological or physical dependence of human beings to drugs. The term addiction is mostly used when talking about strong analgetics. The strong analgetics are used for the alleviation of severe pain, in contrast to weak agents, such as aspirin, acetaminophen or the like. If administered parenterally, they usually show a euphoric effect.

Addiction to barbiturates and strong analgetic agents may develop in the sense of the word "addiction" as defined by the Committee on Problems of Drug Dependence of the National Research Council, known formerly by the name of Drug Addiction Committee of the National Research Council, namely a condition of periodic or chronic intoxication, which damages the individual and the society, produced by the repeated administration of a drug, wherein the characteristic features are the compulsion to take the drug and to increase the dose, together with the development of psychological and sometimes physical dependence on the effects of the drug such that the development of possibilities of continuing the administration of the drug becomes an important motive in the existence of the addict.

Addiction to strong narcotics or narcotic-like analgetics is often found when these substances are administered in a legal, chronic and parenteral way in order to alleviate strong pain. More often, however, addiction to said substances is found when the psychologically unstable individual or an individual seeking adventure is looking for an escape out of the realities of life and finds its escape in euphoria, which is produced by the parenteral administration of strong analgetics. Euphoria is generally defined as a feeling of well-being. Euphoria can be produced by many ways, e.g. by nice events, alcohol, stimulants, anti-depressives, narcotics, etc. For the purposes of describing the present invention, "euphoria" is defined as an abnormal condition of well-being, which is produced by parenteral administration of strong analgetics. The terms "euphoria-producing analgetics" and "strong analgetics", as narcotics or narcotic-like analgetics are termed, are defined when describing the present invention such that they comprise chemical compounds, which, when administered parenterally, uphold or partly uphold an addict, which is known to be addicted to heroine or the like, without substantial withdrawal symptoms. For the purposes of the present invention, a "strong analgetic" is defined as any analgetic composition, whose analgesia-, euphoria- or addiction-producing effects are negated by the parenteral administration of naloxone or one of its salts.

Thus, the object of the present invention is the development of a potent, orally effective but parenterally ineffective analgetic composition, which substantially does not mislead to drug abuse and thus has the effect of preventing analgesia, euphoria or physical dependence, which are produced when an orally effective strong analgetic intended for oral administration is abused by parenteral administration.

Accordingly, the present invention provides an orally effective analgetic composition, which does not produce analgesia, euphoria or physical dependence when administered parenterally, wherein this composition comprises an orally ineffective but parenterally effective dose of naloxone and an orally effective, strong, i.e. narcotic or narcotic-like analgetic agent, in an oral dosage form.

According to the invention, a parenterally effective but orally ineffective dose of naloxone is combined with an orally analgetic dose of an orally effective strong analgetic, wherein the analgetic effect of the analgetic is not impaired when administered orally. If, however, any of the oral dosage forms is in the hands of an addict or a potential addict, the composition will, when injected parenterally, not produce euphoria, but rather specific withdrawal symptoms.

Examples of some representative orally effective strong analgetics and preferred oral dosage ranges of such analgetics are: meperidine (50-250 mg), oxymorphone (5 to 25 mg), alphaprodine (50 to 250 mg), anileridine (25 to 150 mg), dextromoramide (5 to 25 mg), dextropropoxyphene (32 to 150 mg), methadone (5 to 25 mg), metopone (3 to 15 mg), levorphanol (2 to 10 mg), phenazocine (2 to 10 mg), ethoheptazine (100 to 500 mg), propiram (50 to 500 mg), profadol (20 to 250 mg), phenampromide (50 to 250 mg), thiambutene (20 to 150 mg), pentazocine (20 to 200 mg), pholcodeine (25 to 250 mg), codeine (15 to 150 mg), oxycodone (5 to 50 mg), dihydrocodeinone (5 to 100 mg), hydromorphone (10 to 100 mg), fentanyl (0.5 to 10 mg), 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene (50 to 250 mg), 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiophenon-oxime (25 to 150 mg), (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan (10 to 150 mg), (-)-2'-hydroxy-2-(3-methyl-2-

butenyl)-9-methyl-5-phenyl-6,7-benzomorphan (20 to 300 mg), pirinitramide (10 to 150 mg), (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan (50 to 250 mg), 1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate ethylester, (50 to 150 mg), 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine (50 to 500 mg), N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavine (50 to 250 mg), (-)-2'-hydroxy-2-methyl-6,7-benzomorphan (50 to 250 mg), noracylmethadol (10 to 150 mg), phenoperidine (5 to 100 mg), α -dl-methadol (5 to 25 mg), β -dl-methadol (35 to 250 mg), α -l-methadol (2 to 15 mg), β -dl-acetyl methadol (1 to 10 mg), α -l-acetyl methadol (1 to 10 mg), and β -l-acetyl methadol (2 to 25 mg).

When the terms naloxone or the name of a strong analgetic agent are used in order to describe the present invention, all pharmaceutically acceptable non-toxic salts are also comprised and parts of the present invention. The salts of the compounds comprise inter alia the hydrochlorides, sulphates, bisulphates, tartrates, nitrates, citrates, bitartrates, phosphates, malates, maleates, hydrobromides, hydroiodides, fumarates, succinates and the like.

The compositions according to the invention are produced by mixing of an orally ineffective but parenterally effective dose of naloxone with an orally effective strong analgetic. Naloxone and the strong analgetic are preferably combined in amounts of about 0.1 mg to about 10 mg, and most preferably about of 0.1 mg to about 2.5 mg naloxone per analgetic oral dose of the orally effective strong analgetic.

The compositions according to the invention can be formulated in any of the known pharmaceutical forms for oral administration. As such the term "oral dosage form" comprises solid compositions for oral administration in unit dosage forms, such as tablets, capsules, granules, powders, cachets or the like. Bulk powders of fixed compositions for subdivision into therapeutic amounts, solutions, emulsions or suspensions of the composition are also included in the definition.

The compositions according to the invention may also comprise further active ingredients. These include amongst others for example aspirin, phenacetine, caffeine, acetaminophene, antihistamines, homatropine methylbromide, phenyltoloxamine citrate, barbiturates or the like and multiple combinations thereof. Also included within the scope of the present invention are those compositions, which comprise naloxone in combination with antitussive compositions, which contain narcotics or narcotic-like cough suppressing agents such as codeine, dihydrocodeinone, pholcodeine and the like. Other products, which comprise a narcotic or a narcotic-like composition for use as an antispasmodic in the gastrointestinal tract, such as camphorated opium tincture, U.S.P., opium tincture, U.S.P., opium extract, N.F. and the like can also be denaturated with naloxone and they are also part of this invention.

An especially valued composition of the present invention is the oral effective combination of methadone and naloxone. This relies in part on the known and used method of treating addicts with methadone. The regimen of the treatment comprises the oral administration of a maintenance-dose of methadone adequate to prevent narcotic craving, once or several times daily, to the addict. A major disadvantage of the program is that the addict needs to come to a treatment center once a day or several times daily in order to receive the methadone. The oral methadone has to be administered in the presence of a health officer in order to prevent the parenteral abuse for achievement of a euphoric effect. Said disadvantages are avoided by the composition according to the invention. The naloxone-methadone-composition is, as already stated above, orally effective, but cannot be misused parenterally due to the presence of the narcotic-antagonist, naloxone. Thus, it is possible to supply an addict with a supply of a maintenance-dose of methadone for several days without fear of the composition being used for other than that intended.

A preferred embodiment of the present invention is an orally effective, analgetic composition, which does not produce analgesia, euphoria or physical dependence when administered parenterally, wherein the composition comprises an orally ineffective but

parenterally effective dose of naloxone and an orally effective strong analgetic in an oral dosage form.

A preferred embodiment of the present invention is an orally effective, analgetic composition, which does not produce analgesia, euphoria or physical dependence when administered parenterally, wherein the composition contains an orally ineffective but parenterally effective dose of naloxone and an analgetic dose of an orally effective strong analgetic in an oral dosage form.

Another preferred embodiment is an orally effective, analgetic composition, which does not produce analgesia, euphoria or physical dependence when administered parenterally, wherein the composition comprises naloxone and an orally effective, strong analgetic in an oral dosage form and which contains for each analgetic dose of the analgetic agent an amount of naloxone, which is sufficient to negate the analgetic and euphoric action of the compound when the oral dosage form is administered parenterally.

Another preferred embodiment is an orally effective, analgetic composition, which does not produce analgesia, euphoria or physical dependence when administered parenterally, wherein the composition comprises naloxone and an analgetic, which is selected from meperidine, oxymorphone, alphaprodine, anileridine, dextromoramide, dextropropoxyphene, methadone, metopone, levorphanol, phenazocine, ethoheptazine, propiram, profadol, phenampromide, thiambutene, pentazocine, pholcodeine, codeine, oxycodone, dihydrocodeinone, hydromorphone, fentanyl, 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiphenon-oxime, (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, pirinitramide, (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, ethyl 1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-

nororipavin, (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, noracyl methadol, phenoperidine, α -dl-methadol, β -dl-methadol, α -l-methadol, β -dl-acetyl methadol, α -l-acetyl methadol or β -l-acetyl methadol in an oral dosage form, and which contains for each analgetic dose of the analgetic agent a sufficient amount of naloxone in order to negate the analgetic and euphoric action of the composition when the dosage form is administered parenterally.

A more preferred embodiment is an orally effective, analgetic composition, which does not produce analgesia, euphoria or physical dependence when administered parenterally, wherein the composition contains 1 weight-part naloxone per 40 to 400 weight-parts meperidine, 0.4 to 4 weight-parts oxymorphone, 13 to 130 weight-parts alphaprodine, 12 to 120 weight-parts anileridine, 2 to 20 weight-parts dextromoramide, 12 to 120 weight-parts dextropropoxyphene, 2.5 to 25 weight-parts methadone, 0.3 to 3 weight-parts metopone, 0.8 to 8 weight-parts levorphanol, 0.8 to 8 weight-parts phenazocine, 60 to 600 weight-parts ethoheptazine, 20 to 200 weight-parts propiram, 8 to 80 weight-parts profadol, 40 to 400 weight-parts phenampromide, 10 to 100 weight-parts thiambutene, 8 to 80 weight-parts pentazocine, 4 to 40 weight-parts pholcodeine, 15 to 150 weight-parts codeine, 2 to 20 weight-parts oxycodone, 2.5 to 25 weight-parts dihydrocodeinone, 0.8 to 8 weight-parts hydromorphone, 0.1 to 1 weight-parts fentanyl, 15 to 150 weight-parts 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 6 to 60 weight-parts 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiphenon-oxim, 5 to 50 weight-parts (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, 13 to 130 weight-parts (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, 5 to 50 weight-parts pirinitramide, 5 to 50 weight-parts (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, 5 to 50 weight-parts ethyl-1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 20 to 200 weight-parts 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, 0.1 to 1 weight-parts N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavin, 14 to 140 weight-parts (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, 5 to 50 weight-parts noracyl methadol, 2 to 20 weight-parts phenoperidine, 2.5 to 25 weight-parts α -dl-methadol, 40 to 400 weight-parts β -dl-

methadol, 0.3 to 3 weight-parts α -1-methadol, 0.8 to 8 weight-parts β -dl-acetyl methadol, 0.8 to 8 weight-parts α -1-acetyl methadol or 0.4 to 4 weight-parts β -l-acetyl methadol in an oral dosage form.

An embodiment of the present invention is an orally effective, analgetic composition, which does not produce analgesia, euphoria or physical dependence when administered parenterally, wherein the composition comprises about 0.1 mg to about 10 mg naloxone per analgetic oral dose of an orally effective, strong analgetic in an oral unit dosage form.

A preferred embodiment of the present invention is an orally effective, analgetic composition, which does not produce analgesia, euphoria or physical dependence when administered parenterally, and which comprises about 0.1 mg to about 2.5 mg naloxone per analgetic oral dose of an orally effective, strong analgetic in an oral dosage form.

Another preferred embodiment is an orally effective, analgetic composition, which does neither produce analgesia nor euphoria when administered parenterally, wherein the composition comprises about 0.1 mg to about 2.5 mg naloxone per analgetic oral dose of an analgetic selected from meperidine, oxymorphone, alphaprodine, anileridine, dextromoramide, dextropropoxyphene, methadone, metopone, levorphanol, phenazocine, ethoheptazine, propiram, profadol, phenampromide, thiambutene, pentazocine, pholcodeine, codeine, oxycodone, dihydrocodeinone, hydromorphone, fentanyl, 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiophenon-oxime, (-)-8-2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, pirinitramide, (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, ethyl-1-(2-dimethylamino-ethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-etheno-tetrahydro-nororipavin, (-)-2'-hydroxy-2-methyl-6,7-benzomorphan,

noracyl methadol, phenoperidine, α -dl-methadol, β -dl-methadol, α -l-methadol, β -di-acetyl methadol, α -l-acetyl methadol and β -l-acetyl methadol in a unit dosage form.

A preferred embodiment is a composition in a unit dosage form, which comprises 1 mg naloxone for about 2 to about 8 mg phenazocine.

Another preferred embodiment is a composition in a unit dosage form, which comprises 1 mg naloxone for about 5 to about 10 mg methadone.

Another preferred embodiment is a composition in a unit dosage form, which comprises 5 mg naloxone for about 25 to about 50 mg methadone.

Another preferred embodiment is a composition in a unit dosage form, which comprises 1 mg naloxone for about 30 to about 65 mg dextropropoxyphene.

Another preferred embodiment is a composition in a unit dosage form, which comprises 1 mg naloxone for about 2 to about 8 mg levorphanol.

Another preferred embodiment is a composition in a unit dosage form, which comprises 1 mg naloxone for about 10 to about 40 mg profadol.

Another preferred embodiment is a composition in a unit dosage form, which comprises 1 mg naloxone for about 5 to about 25 mg (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan.

Another preferred embodiment is a composition in a unit dosage form, which comprises 1 mg naloxone for about 5 to about 25 mg (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan.

The present invention provides a method for producing analgesia in mammals, which comprises the oral administration of an orally effective analgetic composition, which

does not produce analgesia, euphoria or physical dependence when administered parenterally, wherein the composition comprises an orally ineffective but parenterally effective dose of naloxone and an orally effective strong analgetic in an oral dosage form.

A preferred embodiment of the present invention is the method of producing analgesia in mammals, which comprises the oral administration of an orally effective analgetic composition, which does not produce analgesia, euphoria or physical dependence when administered parenterally, wherein the composition comprises an orally ineffective but parenterally effective dose of naloxone and an analgetic dose of an orally effective strong analgetic in an oral dosage form.

Another preferred embodiment is the method of producing analgesia in mammals, which comprises the oral administration of an orally effective analgetic composition, which does not produce analgesia, euphoria or physical dependence when administered parenterally, wherein the composition comprises naloxone and an orally effective strong analgetic in an oral dosage form and contains a sufficient amount of naloxone per each analgetic dose of the analgetic agent in order to negate the analgesia-, euphoria- and physical dependence-producing action of the composition when the oral dosage form is administered parenterally.

Another preferred embodiment is the method of producing analgesia in humans, which comprises the oral administration of an orally effective analgetic composition, which does not produce analgesia, euphoria or physical dependence when administered parenterally, wherein the composition comprises in an oral dosage form naloxone and an analgetic selected from meperidine, oxymorphone, alphaprodine, anileridine, dextromoramide, dextropropoxyphene, methadone, metopone, levorphanol, phenazocine, etioheptazine, propiram, profadol, phenampromide, thiambutene, pentazocine, pholcodeine, codeine, oxycodone, dihydrocodeinone, hydromorphone, fentanyl, 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiophenon-oxime, (-)- β -2'-

hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, pirinitramide, (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, ethyl-1-(2-dimethylamino-ethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-etheno-tetrahydro-nororipavin, (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, noracetyl methadol, phenoperidine, α -dl-methadol, β -dl-methadol, α -l-methadol, β -dl-acetyl methadol, α -l-acetyl methadol and β -l-acetyl methadol, and which contains for each analgetic dose of the analgetic agent a sufficient amount of naloxone in order to negate the analgetic and euphoric action of the composition when administered parenterally.

Still another preferred embodiment is the method of producing analgesia in a human being, which comprises the oral administration of an analgetic dose of an orally effective analgetic composition, which does not produce analgesia, euphoria or physical dependence when administered parenterally, wherein the composition comprises 1 weight-part naloxone per 40 to 400 weight-parts meperidine, 0.4 to 4 weight-parts oxymorphone, 13 to 130 weight-parts alphaprodine, 12 to 120 weight-parts anileridine, 2 to 20 weight-parts dextromoramide, 12 to 120 weight-parts dextropropoxyphene, 2.5 to 25 weight-parts methadone, 0.3 to 3 weight-parts metopone, 0.8 to 8 weight-parts levorphanol, 0.8 to 8 weight-parts phenazocine, 60 to 600 weight-parts etioheptazine, 20 to 200 weight-parts propiram, 8 to 80 weight-parts profadol, 40 to 400 weight-parts phenampromide, 10 to 100 weight-parts thiambutene, 8 to 80 weight-parts pentazocine, 4 to 40 weight-parts pholcodeine, 15 to 150 weight-parts codeine, 2 to 20 weight-parts oxycodone, 2.5 to 25 weight-parts dihydrocodeinone, 0.8 to 8 weight-parts hydromorphone, 0.1 to 1 weight-parts fentanyl, 15 to 150 weight-parts 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 6 to 60 weight-parts 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiophenon-oxime, 5 to 50 weight-parts (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, 13 to 130 weight-parts (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, 5 to 50 weight-parts pirinitramide, 5 to 50 weight-parts (-)- α -5,9-diethyl-2'-hydroxy-2-

methyl-6,7-benzomorphan, 5 to 50 weight-parts ethyl-1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 20 to 200 weight-parts 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, 0.1 to 1 weight-parts N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavin, 14 to 140 weight-parts (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, 5 to 50 weight-parts noracetyl methadol, 2 to 20 weight-parts phenoperidine, 2.5 to 25 weight-parts α -di-methadol, 40 to 400 weight-parts β -di-methadol, 0.3 to 3 weight-parts α -1-methadol, 0.8 to 8 weight-parts β -di-acetyl methadol, 0.8 to 8 weight-parts α -1-acetyl methadol or 0.4 to 4 weight-parts β -1-acetyl methadol in an oral dosage form.

One embodiment is the method of producing analgesia in mammals, most preferably in humans, which comprises the oral administration of an orally effective analgetic composition, which does not produce analgesia, euphoric or physical dependence when administered parenterally, wherein the composition comprises about 0.1 mg to about 10 mg naloxone per analgetic oral dose of an orally effective, strong analgetic in an oral unit dosage form.

One embodiment is the method of producing analgesia in mammals, most preferably in humans, which comprises the oral administration of an orally effective analgetic composition, which does not produce analgesia, euphoric or physical dependence when administered parenterally, wherein the composition comprises about 0.1 mg to about 2.5 mg naloxone per analgetic oral dose of an orally effective, strong analgetic in an oral unit dosage form.

A highly preferred embodiment is the method of producing analgesia in humans, which comprises the oral administration of an orally effective analgetic composition, which does not produce analgesia, euphoric or physical dependence when administered parenterally, wherein the composition comprises in an oral dosage form about 0.1 mg to about 2.5 mg naloxone per analgetic oral dose of an analgetic selected from meperidine, oxymorphone, alphaprodine, anileridine, dextromoramide, dextropropoxyphene, methadone, metopone, levorphanol, phenazocine, etioheptazine, propiram, profadol,

phenampromide, thiambutene, pentazocine, pholcodeine, codeine, oxycodone, dihydrocodeinone, hydromorphone, fentanyl, 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiofenon-oxime, (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, pirinitramide, (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, ethyl-1-(2-dimethylamino-ethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-etheno-tetrahydro-nororipavin, (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, noracyl methadol, phenoperidine, α -dl-methadol, β -dl-methadol, α -l-methadol, β -dl-acetyl methadol, α -l-acetyl methadol and β -l-acetyl methadol.

The amount-ratios of naloxone to the analgetic agents in compositions according to the invention have either been determined from the literature or in our laboratories. It was found that the parenteral administration of 1 weight-part naloxone will effectively and reliably negate and counteract, respectively, the parenteral effect of up to about 400 weight-parts meperidine, 4 weight-parts oxymorphone, 130 weight-parts alphaprodine, 120 weight-parts anileridine, 20 weight-parts dextromoramide, 120 weight-parts dextropropoxyphene, 25 weight-parts methadone, 3 weight-parts metopone, 8 weight-parts levorphanol, 8 weight-parts phenazocine, 600 weight-parts ethoheptazine, 200 weight-parts propiram, 80 weight-parts profadol, 400 weight-parts phenampromide, 100 weight-parts thiambutene, 80 weight-parts pentazocine, 40 weight-parts pholcodeine, 150 weight-parts codeine, 20 weight-parts oxycodone, 25 weight-parts dihydrocodeinone, 8 weight-parts hydromorphone, 1 weight-parts fentanyl, 150 weight-parts 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 60 weight-parts 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiofenon-oxime, 50 weight-parts (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, 130 weight-parts (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, 50 weight-parts pirinitramide, 50 weight-parts (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, 50 weight-parts ethyl-1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-

methyl-4-oxo-6-phenylindol-2-carboxylate, 200 weight-parts 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, 1 weight-parts N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavin, 140 weight-parts (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, 50 weight-parts noracetyl methadol, 20 weight-parts phenoperidine, 25 weight-parts α -dl-methadol, 400 weight-parts β -dl-methadol, 3 weight-parts α -l-methadol, 8 weight-parts β -dl-acetyl methadol, 8 weight-parts α -l-acetyl methadol or 4 weight-parts β -l-acetyl methadol.

It was also found that naloxone may be administered orally in amounts of up to about the 10-fold minimal parenteral dose, which is necessary to abolish the parenteral action of the analgetic, without abolishing the oral action of the analgetic, e.g. 1 part naloxone per 40 parts meperidine, 1 part naloxone per 0.8 parts phenazocine, etc.

Starting from these parenteral ratios, which define the minimal effective and reliable parenteral dose of naloxone, which is necessary to negate the parenteral dose of the analgetic agent, further experiments have been carried out in order to determine the largest practical and economical amount of naloxone, which can be administered orally per oral therapeutic dose of the analgetic agent without abolishing the oral effect of the analgetic agent. It was found that one can safely administer naloxone orally in amounts of up to about the 10-fold minimal parenteral dose, which is necessary to negate the parenteral action of the orally effective dose of the analgetic. It is emphasized that it is frequently possible to orally administer more than the 10-fold minimal parenteral dose of naloxone without abolishing the oral analgetic effect.

In order to determine the naloxone/analgetic-ratios of some of the euphoria-producing analgetic agents, the "rat-tail-flick"-method is used when carrying out the tests. The method used is the method originally described by D'Amour and Smith (J. Pharmacol. Exper. Therap. 72:74, 1941), wherein a heat-lamp is focussed onto a rat's tail and wherein the time between the onset of the light and a flick of the tail is measured. The method comprises the animal either wrapped in a towel or held in a box wherein the tail lies in a V-shaped groove. The light and the timer are connected in series with a switch

such that both the light and the clock can be switched on and switched off at the same time. When the rat is calming down, the light and the timer are switched on and one awaits the reaction consisting of a characteristic flick of the tail. The untreated rat usually reacts after about 3.5 seconds. Rats weighing between 160 and 190 g have been found most uniform in response in the control animals and in the treated animals.

An example of such a test is the subsequently described determination of the parenteral ratio for oxymorphone in rats. Untreated rats show the desired tail-flick after 3.5 seconds. A differing amount of oxymorphone hydrochloride is administered subcutaneously to a number of rats in order to determine the minimal amount of oxymorphone hydrochloride, which is necessary to delay the tail-flick to 7 seconds. The required amount is 0.22 mg/kg body weight.

A number of rats treated this way with oxymorphone hydrochloride are then treated with different doses of subcutaneously administered naloxone hydrochloride in order to determine the minimal amount of naloxone, which completely negates the analgesia produced by oxymorphone. The required amount is 0.025 mg/kg body weight.

Thus, the parenteral naloxone/analgetic-ratio is therefore approximately 1 part naloxone hydrochloride to about 9 parts oxymorphone hydrochloride.

After having established that the parenteral administration of 1 part naloxone completely negates the analgetic action of about 9 parts oxymorphone, the ratio was subsequently determined for the oral administration of the combination.

Differing amounts of oxymorphone are administered via a stomach tube to a number of starved rats in order to determine the oral dose of oxymorphone, which is necessary to produce a "tail-flick" within 7 seconds. The dose of oxymorphone hydrochloride was dissolved in 20 ml water per kg body weight. It was determined that 50 mg/kg given orally result in the desired tail-flick in 6 out of 6 rats. A dose of 25 mg/kg results in the desired effect in 5 out of 6 rats.

A composition of 1.1 g naloxone hydrochloride and oxymorphone hydrochloride is prepared, which comprises 0.1 g of naloxone-HCl and 1.0 g of oxymorphone-HCl (ratio of 1:10).

A dose of 27.5 mg/kg body weight of the above composition, dissolved in 20 ml water, is administered via a stomach tube. 6 out of 6 rats show a tail-flick-reaction after at least 7 seconds. When a dose of 55 mg/kg is administered, 6 out of 6 rats again show the analgetic effect after at least 7 seconds.

In an experiment similar to the above, it could be determined that 50 mg/kg phenazocine given orally produced the desired tail-flick-reaction in 5 out of 6 rats. A dose of 100 mg/kg produced the desired reaction in 6 out of 6 rats.

A composition of 0.64 g naloxone hydrochloride and phenazocine hydrobromide is prepared, which comprises 0.04 g of naloxone-HCl and 0.60 g of phenazocine-HBr (ratio of 1:15).

A dose of 53.3 mg/kg body weight of the above composition, dissolved in 20 ml water, is administered via a stomach tube. 6 out of 6 rats show a tail-flick-reaction after at least 7 seconds. When a dose of 106.6 mg/kg is administered, again 6 out of 6 rats show the desired analgetic effect after at least 7 seconds.

It was found in further experiments with phenazocine-HBr that compositions, which contain naloxone-doses in 100% excess over the minimal antagonistic parenteral dose, still produce analgesia when administered orally.

Thus, a parenteral antagonistic dose of naloxone can be administered orally without interfering with the analgetic effect of the orally administered analgetic.

There is the possibility of different naloxone-analgetic-ratios due to differences of the species, e.g. rat compared to man. Our laboratory experiments show for instance that 1 part of parenterally administered naloxone-hydrochloride negates the analgetic effect of about 9 parts of parenterally administered oxymorphone hydrochloride in rats. In the literature, however, it is described that 1 part of naloxone-HCl is required parenterally in order to negate the analgetic effect of 4 parts of oxymorphone-HCl parenterally in man.

Likewise, it was found that 1 part naloxone parenterally negates the effect of about 15 parts phenazocine-HBr in rats, whereas it is known from the literature that 1 part naloxone parenterally is required in order to negate the effect of 8 parts phenazocine-HBr parenterally in man.

Description of the preferred embodiments

Example 1

Naloxone-hydrochloride	0.10 g
Methadone-hydrochloride	0.500 g
Lactose, as much as required for	100 capsules

Example 2

Naloxone-hydrochloride	1.0 g
Phenazocine-hydrobromide	2.5 g
Magnesium stearate and	
Maize starch, as much as required for	1000 tablets

Example 3

Naloxone-hydrochloride	0.050 g
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Meperidine-hydrochloride	5.0 g
Maize starch and	
Talcum (aa), as much as required for	100 capsules

Example 4

Naloxone-hydrochloride	0.5 g
Methadone-hydrochloride	5.0 g
Lactose, as much as required for	100 capsules

Example 5

Naloxone-hydrochloride	0.4 g
Codeine sulphate	30 g
Magnesium stearate and	
Maize starch, as much as required for	1000 tablets

Example 6

Naloxone-hydrochloride	1.0 g
Dextropropoxyphene hydrochloride	65.0 g
Lactose, as much as required for	1000 capsules

Example 7

Naloxone (or one of its salts)	0.050 g
Camphorated opium tincture U.S.P.	
as much as required for	100 ml

Example 8

Naloxone-hydrobromide	1.0 g
Levorphanol	6.0 g
Lactose, as much as required for	1000 capsules

Example 9

Naloxone-hydrobromide	0.10 g
Profadol	2.0 g
Lactose, as much as required for	100 capsules

Example 10

Naloxone-hydrochloride	1.0 g
(-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan	10.0 g
Lactose, as much as required for	1000 capsules

Example 11

Naloxone	0.10 g
(-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan	1.0 g
Lactose, as much as required for	100 capsules

Example 12

Naloxone-hydrochloride	0.1 g
Oxymorphone-HCl	1.0 g
Lactose, as much as required for	100 capsules

The compounds used according to the invention are chemically identified in Merck Index, 8th edition. Profadol is chemically m-(1-methyl-3-propyl-3-pyrrolidinyl)-phenol (Journal Pharm. Exp. Ther. 154, page 161). Ethoheptacine is described in Merck Index, page 428.

Claims

1. Method of manufacturing an orally effective analgetic composition in an oral dosage form, which does not produce analgesia, euphoria or physical dependence when administered parenterally, characterized in that an orally ineffective but parenterally effective dose of naloxone is mixed with an orally effective strong analgetic.
2. Method according to claim 1, characterized in that the analgetic is meperidine, oxymorphone, alphaprodine, anileridine, dextromoramide, dextropropoxyphene, methadone, metopone, levorphanol, phenazocine, etoheptazine, propiram, profadol, phenampromide, thiambutene, pentazocine, pholcodeine, codeine, oxycodone, dihydrocodeinone, hydromorphone, fentanyl, 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiophenon-oxime, (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, pirinitramide, (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, ethyl 1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavin, (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, noracyl methadol, phenoperidine, α -dl-methadol, β -dl-methadol, α -l-methadol, β -dl-acetyl methadol, α -l-acetyl methadol or β -l-acetyl methadol.
3. Method according to claim 2, characterized in that naloxone and analgetic are used in a weight-ratio of 1 weight-part naloxone per 40 to 400 weight-parts meperidine, 0.4 to 4 weight-parts oxymorphone, 13 to 130 weight-parts alphaprodine, 12 to 120 weight-parts anileridine, 2 to 20 weight-parts dextromoramide, 12 to 120 weight-parts dextropropoxyphene, 2.5 to 25 weight-parts methadone, 0.3 to 3 weight-parts metopone, 0.8 to 8 weight-parts levorphanol, 0.8 to 8 weight-parts phenazocine, 60 to 600 weight-parts etoheptazine, 20 to 200 weight-parts propiram, 8 to 80 weight-parts profadol, 40 to 400 weight-parts phenampromide, 10 to 100 weight-parts thiambutene, 8 to 80 weight-

parts pentazocine, 4 to 40 weight-parts pholcodeine, 15 to 150 weight-parts codeine, 2 to 20 weight-parts oxycodone, 2.5 to 25 weight-parts dihydrocodeinone, 0.8 to 8 weight-parts hydromorphone, 0.1 to 1 weight-parts fentanyl, 15 to 150 weight-parts 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 6 to 60 weight-parts 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiophenon-oxim, 5 to 50 weight-parts (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, 13 to 130 weight-parts (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, 5 to 50 weight-parts pirinitramide, 5 to 50 weight-parts (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, 5 to 50 weight-parts ethyl-1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 20 to 200 weight-parts 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, 0.1 to 1 weight-parts N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavin, 14 to 140 weight-parts (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, 5 to 50 weight-parts noracetyl methadol, 2 to 20 weight-parts phenoperidine, 2.5 to 25 weight-parts α -dl-methadol, 40 to 400 weight-parts β -dl-methadol, 0.3 to 3 weight-parts α -l-methadol, 0.8 to 8 weight-parts β -dl-acetyl methadol, 0.8 to 8 weight-parts α -l-acetyl methadol or 0.4 to 4 weight-parts β -l-acetyl methadol.

4. Method of manufacturing an orally effective analgetic composition in an oral unit dosage form, which does not produce analgesia, euphoria or physical dependence when administered parenterally, characterized in that about 0.1 mg to about 10 mg of naloxone are mixed with an analgetic oral dose of an orally effective strong analgetic.

5. Method according to claim 4, characterized in that, about 0.1 mg to about 2.5 mg naloxone are mixed with an analgetic oral dose of an orally effective, strong analgetic.

6. Method according to claim 4 or 5, characterized in that the analgetic is meperidine, oxymorphone, alphaprodine, anileridine, dextromoramide, dextropropoxyphene, methadone, metopone, levorphanol, phenazocine, etioheptazine, propiram, profadol, phenampromide, thiambutene, pentazocine, pholcodeine, codeine,

oxycodone, dihydrocodeinone, hydromorphone, fentanyl, 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiphenon-oxime, (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, pirinitramide, (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, ethyl 1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavine, (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, noracetyl methadol, phenoperidine, α -di-methadol, β -di-methadol, α -1-methadol, β -di-acetyl methadol, α -1-acetyl methadol or β -1-acetyl methadol.

7. Method according to any of claims 1 to 6, characterized in that the analgetic is methadone, phenazocine, meperidine, codeine, dextropropoxyphene, camphorated opium tincture, levorphanol, profadol, oxymorphone, (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan or (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan.

8. Method of manufacturing an orally effective analgetic composition in an oral dosage form, which substantially does not provide a possibility of drug abuse, characterized in that an orally ineffective but parenterally effective dose of naloxone is mixed with an analgetic dose of an orally effective strong analgetic.

9. Method according to claim 8, characterized in that the analgetic is meperidine, oxymorphone, alphaprodine, anileridine, dextromoramide, dextropropoxyphene, methadone, metopone, levorphanol, phenazocine, ethoheptazine, propiram, profadol, phenampromide, thiambutene, pentazocine, pholcodeine, codeine, oxycodone, dihydrocodeinone, hydromorphone, fentanyl, 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiphenon-oxime, (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, pirinitramide, (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, ethyl 1-(2-

dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavin, (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, noracyl methadol, phenoperidine, α -dl-methadol, β -dl-methadol, α -l-methadol, β -dl-acetyl methadol, α -l-acetyl methadol or β -l-acetyl methadol.

10. Method according to claim 9, characterized in that naloxone and analgetic are used in a weight ratio of 1 weight-part naloxone per 40 to 400 weight-parts meperidine, 0.4 to 4 weight-parts oxymorphone, 13 to 130 weight-parts alphaprodine, 12 to 120 weight-parts anileridine, 2 to 20 weight-parts dextromoramide, 12 to 120 weight-parts dextropropoxyphene, 2.5 to 25 weight-parts methadone, 0.3 to 3 weight-parts metopone, 0.8 to 8 weight-parts levorphanol, 0.8 to 8 weight-parts phenazocine, 60 to 600 weight-parts etoheptazine, 20 to 200 weight-parts propiram, 8 to 80 weight-parts profadol, 40 to 400 weight-parts phenampromide, 10 to 100 weight-parts thiambutene, 8 to 80 weight-parts pentazocine, 4 to 40 weight-parts pholcodeine, 15 to 150 weight-parts codeine, 2 to 20 weight-parts oxycodone, 2.5 to 25 weight-parts dihydrocodeinone, 0.8 to 8 weight-parts hydromorphone, 0.1 to 1 weight-parts fentanyl, 15 to 150 weight-parts 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 6 to 60 weight-parts 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiofenon-oxime, 5 to 50 weight-parts (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, 13 to 130 weight-parts (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, 5 to 50 weight-parts pirinitramide, 5 to 50 weight-parts (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, 5 to 50 weight-parts ethyl-1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 20 to 200 weight-parts 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, 0.1 to 1 weight-parts N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavin, 14 to 140 weight-parts (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, 5 to 50 weight-parts noracyl methadol, 2 to 20 weight-parts phenoperidine, 2.5 to 25 weight-parts α -dl-methadol, 40 to 400 weight-parts β -dl-methadol, 0.3 to 3 weight-parts α -l-methadol, 0.8 to 8 weight-parts β -dl-acetyl

methadol, 0.8 to 8 weight-parts α -1-acetyl methadol or 0.4 to 4 weight-parts β -1-acetyl methadol.

11. Method of preventing drug abuse by parenteral administration of an orally effective strong analgetic, characterized in that the orally effective strong analgetic is combined with an orally ineffective but parenterally effective dose of naloxone.

12. Method according to claim 11, characterized in that the analgetic is meperidine, oxymorphone, alphaprodine, anileridine, dextromoramide, dextropropoxyphene, methadone, metopone, levorphanol, phenazocine, etoheptazine, propiram, profadol, phenampromide, thiambutene, pentazocine, pholcodeine, codeine, oxycodone, dihydrocodeinone, hydromorphone, fentanyl, 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ' -cyclohexene, 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiophenon-oxime, (-)-8-2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, pirinitramide, (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, ethyl 1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavin, (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, noracyl methadol, phenoperidine, α -dl-methadol, β -dl-methadol, α -1-methadol, β -dl-acetyl methadol, α -1-acetyl methadol or β -1-acetyl methadol.

13. Method according to claim 12, characterized in that naloxone and analgetic are used in a weight ratio of 1 weight-part naloxone per 40 to 400 weight-parts meperidine, 0.4 to 4 weight-parts oxymorphone, 13 to 130 weight-parts alphaprodine, 12 to 120 weight-parts anileridine, 2 to 20 weight-parts dextromoramide, 12 to 120 weight-parts dextropropoxyphene, 2.5 to 25 weight-parts methadone, 0.3 to 3 weight-parts metopone, 0.8 to 8 weight-parts levorphanol, 0.8 to 8 weight-parts phenazocine, 60 to 600 weight-parts etoheptazine, 20 to 200 weight-parts propiram, 8 to 80 weight-parts profadol, 40 to 400 weight-parts phenampromide, 10 to 100 weight-parts thiambutene, 8 to 80 weight-

parts pentazocine, 4 to 40 weight-parts pholcodeine, 15 to 150 weight-parts codeine, 2 to 20 weight-parts oxycodone, 2.5 to 25 weight-parts dihydrocodeinone, 0.8 to 8 weight-parts hydromorphone, 0.1 to 1 weight-parts fentanyl, 15 to 150 weight-parts 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 6 to 60 weight-parts 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiphenon-oxim, 5 to 50 weight-parts (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, 13 to 130 weight-parts (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, 5 to 50 weight-parts pirinitramide, 5 to 50 weight-parts (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, 5 to 50 weight-parts ethyl-1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 20 to 200 weight-parts 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, 0.1 to 1 weight-parts N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavin, 14 to 140 weight-parts (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, 5 to 50 weight-parts noracetyl methadol, 2 to 20 weight-parts phenoperidine, 2.5 to 25 weight-parts α -dl-methadol, 40 to 400 weight-parts β -dl-methadol, 0.3 to 3 weight-parts α -l-methadol, 0.8 to 8 weight-parts β -dl-acetyl methadol, 0.8 to 8 weight-parts α -l-acetyl methadol or 0.4 to 4 weight-parts β -l-acetyl methadol.

14. Method of preventing analgesia, euphoria or physical dependence when an orally effective strong analgetic intended for oral administration is abused by parenteral administration, characterized in that an orally ineffective but parenterally effective dose of naloxone is combined with an orally effective strong analgetic.

15. Method according to claim 14, characterized in that the analgetic is meperidine, oxymorphone, alphaprodine, anileridine, dextromoramide, dextropropoxyphene, methadone, metopone, levorphanol, phenazocine, ethoheptazine, propiram, profadol, phenampromide, thiambutene, pentazocine, pholcodeine, codeine, oxycodone, dihydrocodeinone, hydromorphone, fentanyl, 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiphenon-oxime, (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, (-)-

2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, pirinitramide, (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, ethyl 1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavin, (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, noracyl methadol, phenoperidine, α -dl-methadol, β -dl-methadol, α -l-methadol, β -dl-acetyl methadol, α -l-acetyl methadol or β -l-acetyl methadol.

16. Method according to claim 15, characterized in that naloxone and analgetic are used in a weight ratio of 1 weight-part naloxone per 40 to 400 weight-parts meperidine, 0.4 to 4 weight-parts oxymorphone, 13 to 130 weight-parts alphaprodine, 12 to 120 weight-parts anileridine, 2 to 20 weight-parts dextromoramide, 12 to 120 weight-parts dextropropoxyphene, 2.5 to 25 weight-parts methadone, 0.3 to 3 weight-parts metopone, 0.8 to 8 weight-parts levorphanol, 0.8 to 8 weight-parts phenazocine, 60 to 600 weight-parts etoheptazine, 20 to 200 weight-parts propiram, 8 to 80 weight-parts profadol, 40 to 400 weight-parts phenampromide, 10 to 100 weight-parts thiambutene, 8 to 80 weight-parts pentazocine, 4 to 40 weight-parts pholcodeine, 15 to 150 weight-parts codeine, 2 to 20 weight-parts oxycodone, 2.5 to 25 weight-parts dihydrocodeinone, 0.8 to 8 weight-parts hydromorphone, 0.1 to 1 weight-parts fentanyl, 15 to 150 weight-parts 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 6 to 60 weight-parts 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiophenon-oxim, 5 to 50 weight-parts (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, 13 to 130 weight-parts (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, 5 to 50 weight-parts pirinitramide, 5 to 50 weight-parts (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, 5 to 50 weight-parts ethyl-1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 20 to 200 weight-parts 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, 0.1 to 1 weight-parts N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavin, 14 to 140 weight-parts (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, 5 to 50 weight-parts noracyl methadol, 2 to 20 weight-parts

phenoperidine, 2.5 to 25 weight-parts α -di-methadol, 40 to 400 weight-parts β -di-methadol, 0.3 to 3 weight-parts α -1-methadol, 0.8 to 8 weight-parts β -di-acetyl methadol, 0.8 to 8 weight-parts α -1-acetyl methadol or 0.4 to 4 weight-parts β -1-acetyl methadol.

17. Orally effective analgetic composition, which does not produce analgesia, euphoria or physical dependence when administered parenterally, characterized in that the composition comprises an orally ineffective but parenterally effective dose of naloxone and an orally effective strong analgetic in an oral dosage form.

18. Orally effective analgetic composition, which does not produce analgesia, euphoria or physical dependence when administered parenterally, characterized in that the composition comprises an orally ineffective but parenterally effective dose of naloxone and an analgetic dose of an orally effective strong analgetic in an oral dosage form.

19. Orally effective analgetic composition, which does not produce analgesia, euphoria or physical dependence when administered parenterally, characterized in that the composition comprises naloxone and an orally effective strong analgetic in an oral dosage form and contains a sufficient amount of naloxone for each analgetic dose of the analgetic agent in order to negate the analgetic and euphoric effect of the composition when the oral dosage form is administered parenterally.

20. Composition according to claim 19, characterized in that the composition comprises 1 weight-part naloxone per 40 to 400 weight-parts meperidine, 0.4 to 4 weight-parts oxymorphone, 13 to 130 weight-parts alphaprodine, 12 to 120 weight-parts anileridine, 2 to 20 weight-parts dextromoramide, 12 to 120 weight-parts dextropropoxyphene, 2.5 to 25 weight-parts methadone, 0.3 to 3 weight-parts metopone, 0.8 to 8 weight-parts levorphanol, 0.8 to 8 weight-parts phenazocine, 60 to 600 weight-parts etoheptazine, 20 to 200 weight-parts propiram, 8 to 80 weight-parts profadol, 40 to 400 weight-parts phenampromide, 10 to 100 weight-parts thiambutene, 8 to 80 weight-

parts pentazocine, 4 to 40 weight-parts pholcodeine, 15 to 150 weight-parts codeine, 2 to 20 weight-parts oxycodone, 2.5 to 25 weight-parts dihydrocodeinone, 0.8 to 8 weight-parts hydromorphone, 0.1 to 1 weight-parts fentanyl, 15 to 150 weight-parts 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ' -cyclohexene, 6 to 60 weight-parts 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiofenon-oxim, 5 to 50 weight-parts (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, 13 to 130 weight-parts (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, 5 to 50 weight-parts piritramide, 5 to 50 weight-parts (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, 5 to 50 weight-parts ethyl-1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 20 to 200 weight-parts 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, 0.1 to 1 weight-parts N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavin, 14 to 140 weight-parts (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, 5 to 50 weight-parts noracetyl methadol, 2 to 20 weight-parts phenoperidine, 2.5 to 25 weight-parts α -dl-methadol, 40 to 400 weight-parts β -dl-methadol, 0.3 to 3 weight-parts α -l-methadol, 0.8 to 8 weight-parts β -dl-acetyl methadol, 0.8 to 8 weight-parts α -l-acetyl methadol or 0.4 to 4 weight-parts β -l-acetyl methadol.

21. Orally effective, analgetic composition, which does not produce analgesia, euphoria or a physical dependence when administered parenterally, characterized in that the composition comprises about 0.1 mg to about 10 mg naloxone per analgetic oral dose of an orally effective strong analgetic in an oral unit dosage form.

22. Orally effective analgetic composition, which does not produce analgesia, euphoria or a physical dependence when administered parenterally, characterized in that the composition comprises about 0.1 mg to about 2.5 mg naloxone per analgetic oral dose of an orally effective strong analgetic in an oral unit dosage form.

23. Orally effective analgetic composition, which does not produce analgesia, euphoria or a physical dependence when administered parenterally, characterized in that

the composition comprises about 0.1 mg to about 2.5 mg naloxone per analgetic oral dose of an analgetic selected from meperidine, oxymorphone, alphaprodine, anileridine, dextromoramide, dextropropoxyphene, methadone, metopone, levorphanol, phenazocine, ethioheptazine, propiram, profadol, phenampromide, thiambutene, pentazocine, pholcodeine, codeine, oxycodone, dihydrocodeinone, hydromorphone, fentanyl, 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiophenon-oxime, (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, piritramide, (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, ethyl 1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavin, (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, noracyl methadol, phenoperidine, α -dl-methadol, β -dl-methadol, α -l-methadol, β -dl-acetyl methadol, α -l-acetyl methadol or β -l-acetyl methadol in an oral unit dosage form.

24. Composition according to any of the claims 17 to 23, characterized in that the analgetic is methadone, phenazocine, meperidine, codeine, dextropropoxyphene, camphorated opium tincture, levorphanol, profadol, oxymorphone, (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan or (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan.

25. Composition according to claim 21 characterized in that it comprises 1 mg naloxone for about 2 to about 8 mg phenazocine.

26. Composition according to claim 21 characterized in that it comprises 1 mg naloxone for about 5 to about 10 mg methadone.

27. Composition according to claim 21, characterized in that it comprises 5 mg naloxone for about 25 to about 50 mg methadone.

28. Composition according to claim 21, characterized in that it comprises 1 mg naloxone for about 30 to about 65 mg dextropropoxyphene.
29. Composition according to claim 21, characterized in that it comprises 1 mg naloxone for about 2 to about 8 mg levorphanol.
30. Composition according to claim 21, characterized in that it comprises 1 mg naloxone for about 10 to about 40 mg profadol.
31. Composition according to claim 21, characterized in that it comprises 1 mg naloxone for about 5 to about 25 mg (-)-B-2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan.
32. Composition according to claim 21, characterized in that it comprises 1 mg naloxone per about 5 to about 25 mg (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan.
33. Composition according to claim 21, characterized in that it comprises 1 mg naloxone per about 10 mg oxymorphone.
34. Analgetic composition according to any of the claims 17 to 33, combined with an active ingredient selected from aspirin, phenacetin, caffeine, acetaminophen, antihistamine, homatropine methyl bromide, phenyl tolloxamincitrate, barbiturates or mixtures thereof.
35. Orally effective analgetic composition, which substantially does not provide an option for drug abuse when administered parenterally, characterized in that the composition comprises an orally ineffective but parenterally effective dose of naloxone and an analgetic dose of an orally effective strong analgetic in an oral dosage form.

36. Composition according to claim 35, characterized in that the analgettic is meperidine, oxymorphone, alphaprodine, anileridine, dextromoramide, dextropropoxyphene, methadone, metopone, levorphanol, phenazocine, etioheptazine, propiram, profadol, phenampromide, thiambutene, pentazocine, pholcodeine, codeine, oxycodone, dihydrocodeinone, hydromorphone, fentanyl, 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiofenon-oxime, (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-benzomorphan, pirinitramide, (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, ethyl 1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavin, (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, noracetyl methadol, phenoperidine, α -dl-methadol, β -dl-methadol, α -l-methadol, β -dl-acetyl methadol, α -l-acetyl methadol or β -l-acetyl methadol.

37. Composition according to claim 36, characterized in that the composition comprises 1 weight-part naloxone per 40 to 400 weight-parts meperidine, 0.4 to 4 weight-parts oxymorphone, 13 to 130 weight-parts alphaprodine, 12 to 120 weight-parts anileridine, 2 to 20 weight-parts dextromoramide, 12 to 120 weight-parts dextropropoxyphene, 2.5 to 25 weight-parts methadone, 0.3 to 3 weight-parts metopone, 0.8 to 8 weight-parts levorphanol, 0.8 to 8 weight-parts phenazocine, 60 to 600 weight-parts etioheptazine, 20 to 200 weight-parts propiram, 8 to 80 weight-parts profadol, 40 to 400 weight-parts phenampromide, 10 to 100 weight-parts thiambutene, 8 to 80 weight-parts pentazocine, 4 to 40 weight-parts pholcodeine, 15 to 150 weight-parts codeine, 2 to 20 weight-parts oxycodone, 2.5 to 25 weight-parts dihydrocodeinone, 0.8 to 8 weight-parts hydromorphone, 0.1 to 1 weight-parts fentanyl, 15 to 150 weight-parts 3-trans-dimethylamino-4-phenyl-4-trans-carbethoxy- Δ^1 -cyclohexene, 6 to 60 weight-parts 3-dimethylamino-0-(4-methoxy-phenyl-carbamoyl)-propiofenon-oxim, 5 to 50 weight-parts (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan, 13 to 130 weight-parts (-)-2'-hydroxy-2-(3-methyl-2-butenyl)-9-methyl-5-phenyl-6,7-

benzomorphan, 5 to 50 weight-parts pirinitramide, 5 to 50 weight-parts (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan, 5 to 50 weight-parts ethyl-1-(2-dimethylaminoethyl)-4,5,6,7-tetrahydro-3-methyl-4-oxo-6-phenylindol-2-carboxylate, 20 to 200 weight-parts 1-benzoylmethyl-2,3-dimethyl-3-(m-hydroxyphenyl)-piperidine, 0.1 to 1 weight-parts N-allyl-7 α -(1-(R)-hydroxy-1-methyl-butyl)-6,14-endo-ethenotetrahydro-nororipavin, 14 to 140 weight-parts (-)-2'-hydroxy-2-methyl-6,7-benzomorphan, 5 to 50 weight-parts noracyl methadol, 2 to 20 weight-parts phenoperidine, 2.5 to 25 weight-parts α -dl-methadol, 40 to 400 weight-parts β -dl-methadol, 0.3 to 3 weight-parts α -l-methadol, 0.8 to 8 weight-parts β -dl-acetyl methadol, 0.8 to 8 weight-parts α -l-acetyl methadol or 0.4 to 4 weight-parts β -l-acetyl methadol.

38. Composition according to any of the claims 35 to 37, characterized in that the analgetic is methadone, phenazocine, meperidine, codeine, dextropropoxyphene, camphorated opium tincture, levorphanol, profadol, oxymorphone, (-)- β -2'-hydroxy-2,9-dimethyl-5-phenyl-6,7-benzomorphan or (-)- α -5,9-diethyl-2'-hydroxy-2-methyl-6,7-benzomorphan.